## Remarks

Following entry of this Amendment, claims 34-42 and 44-49 are now pending in the application. Claim 43 was canceled because it claimed subject matter to that of identical claim 42, as amended. Amended claims 34-42 and 44-49 find support in the specification at, inter alia, page 3, line 23 through page 5, line 25.

The Office Action raised several issues to be addressed by Applicants prior to the Examiner's consideration of the pending Request for Interference with respect to U.S. Patent No. 5,476,774. Applicants reply to each of these issues in the order presented in the Office Action. With regard to the newly entered rejections of the claims, to the extent they apply to the claims as amended, they are respectfully traversed for the reasons set forth herein.

**Initial Matter**

The Examiner indicated in the introduction section of the Office Action (see page 4) that the parent application, serial No. 07/148,959, does not provide support for the full scope of the proposed interference count. Applicants submit that the relevant question is whether the claims presented for examination are supported by the disclosure of the application. As discussed in greater detail below, Applicants have amended the claims to limit them to reaction mixtures and kits for the quantitation of an RNA target. The Examiner has acknowledged that the claims, if so limited, would be supported by the disclosure both of this application and parent application 07/148,959.

The proposed count (which corresponds to claim 15 of the Wang '774 patent) is generic with respect to the target nucleic acid. Thus, Applicants' claims, as amended, are directed to a

species encompassed by the count and the '774 claim. The test for interference is set forth in 37 C.F.R. § 601(n). That test is met here. If Applicants' species claims to reaction mixtures for quantitative amplification of RNA targets were treated as prior art, then Wang's genus claim which is directed generally to quantitative amplification of nucleic acid targets would not be patentable under § 102 or § 103. Accordingly, it is respectfully submitted that an interference in fact exists between Applicants' amended claims and the claims of the Wang '774 patent.

**Consideration of Issues Described in the Remand (Parts I-V)**

With regard to Parts I and II, Applicants acknowledge and appreciate the Examiner's withdrawal of the potential § 102(e) and obviousness-type double patenting rejections based on U.S. Patent No. 5,622,820.

Part III requires no response by Applicants (regarding canceled claim 18).

With regard to Part IV, Applicants agree with the Examiner's summary of the relationship between the instant application and its parent applications. See Office Action at page 9.

With regard to Part V, Applicants again acknowledge and appreciate the Patent Office's grant of the petition to accept the instant application without drawings.

**New Grounds for Rejection of the Claims**

A. Rejection Under 35 U.S.C. § 112, first paragraph

Claims 34-41 and 46-49 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not adequately described in the specification. The Examiner asserts that the claims contain new matter because the original disclosure was limited to the

amplification of viral RNA. Applicants have amended claims 34-41 and 46-49 to limit their scope to the quantitation of target RNA after amplification. The purpose of this amendment is to obviate the rejection under § 112 based on lack of written descriptive support. As acknowledged in the Office Action at page 3, the present specification and parent application 07/148,959 (filed 1/27/88), disclose viral RNA embodiments. Therefore, the claims as amended fully comply with 35 U.S.C. § 112, first paragraph, and Applicants respectfully request that the rejection be reconsidered and withdrawn.

B. Rejection Under 35 U.S.C. § 112, second paragraph

Claims 36, 40 and 44 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner asserts that claim 36 is indefinite because it does not recite a limitation that the resultant products of amplification of the control sequences versus the target sequences are distinguishable either by size or by use of an internal oligonucleotide probe. Applicants have amended claim 36 to add a limitation that the products of the amplification of the control sequences and the target sequences are distinguishable by size or by use of an internal oligonucleotide probe. Therefore, Applicants believe that rejection has been overcome, and respectfully request that it be reconsidered and withdrawn.

C. Rejection Under 35 U.S.C. § 102(b)

Claim 49 was rejected under 35 U.S.C. § 102 (b) as anticipated by U.S. patent 5,219,727 to Wang et al. ("Wang"). The Wang patent issued on June 15, 1993, and claims on its face application priority dating back to August 21, 1989.

The Examiner asserts that Wang discloses a method of amplification which utilizes an internal standard or control sequence for quantitation of target nucleic acid wherein the same primers will amplify both the target nucleic acid as well as the internal standard or control sequence. The Examiner noted that, unlike claims previously in the application as filed, claim 49, as filed on December 19, 1996, is not limited to viral RNA, but rather is generic regarding target nucleic acids. "This increased scope supports this rejection under 35 U.S.C. § 102(b) as the embodiments directed to non-viral RNA target nucleic acid or DNA (any target) are not filed within the required one year after issuance of said Wang et al. Patent Number 5,219,727." Office Action at page 12, second full paragraph.

Claim 49, as amended herein, is directed to a method for the quantitative determination of a target RNA sequence, comprising simultaneously amplifying the target RNA sequence and a predetermined amount of a control sequence, the control sequence being capable of amplification by the same oligonucleotide primers used for amplification of the target RNA sequence, and quantifying the amount of the target RNA sequence in the sample using the control sequence as an internal standard.

Claim 49 is entitled to an application priority date based on the filing of parent application number 07/148,959 (filed January 27, 1988). At page 3 of the Office Action, the Examiner acknowledges that the '959 application discloses viral RNA embodiments. Because claim 49 is entitled to an effective filing date of January 27, 1988, Wang's '727 patent is not prior art to the subject matter of claim 49.

Therefore, Applicants submit that this rejection has been obviated and respectfully request that it be reconsidered and withdrawn.

D. Rejection Under 35 U.S.C. § 102(b) and (e)

Claims 36, 37, 40, 41 and 48 were rejected under 35 U.S.C. § 102 (b) and (e) as anticipated by U.S. patent 4,683,195 to Mullis et al. ("Mullis"), which issued on July 28, 1987.

The Examiner asserts that Mullis discloses PCR amplification primers synthesized for pBR328 segment amplification, and that various reaction mixtures were prepared using the same primers with different target nucleic acids. The Examiner further asserts that the target nucleic acid sequences pBR328:HbA and pBR328:HbS are amplified with the same primers and serve as control sequences compared to MstII restriction enzyme digested plasmids. See Office Action at p. 13, lines 12-22. Further, it is asserted that while Mullis may not disclose a kit per se as required by claim 36, "[i]t is inherently required that the disclosure of adding these components occurs from separate individual containers," and that the quantification limitation in the preamble "is deemed a product by process limitation which does not prevent this rejection in that the product may also be used in the method of Mullis et al. even though it also has the use for quantitation methodology." Office Action at p. 14, lines 1-8 and p. 15, lines 28-29.

Claim 36 is directed essentially to a kit for the quantitation of a target RNA segment comprising individual containers which provide (a) a predetermined initial amount of a control sequence for quantitation of a target RNA wherein the control sequence binds the same primers as are bound by the target RNA segment; and (b) an oligonucleotide primer pair wherein the

primer pair can serve to amplify the control sequence and the target RNA, wherein following amplification the control sequence and target amplified RNA segments are distinguishable by size or by use of an internal oligonucleotide probe.

As the Examiner acknowledges (see Section E below), Mullis does not disclose kits. Applicants submit that nothing in Mullis suggests providing a control sequence and primer pair in kit form, as required by claim 36 et seq. Mullis simply conducted six reactions in parallel to determine whether MstII digestion could be used to distinguish the $b^A$ and $b^S$ alleles of a cloned β-globin gene. In the absence of a teaching by Mullis to use a control sequence for quantitation of a target sequence, there was no suggestion to put in kit form a control sequence and primer pair. It is axiomatic that such suggestion cannot be derived from Applicants' own disclosure.

The Mullis patent relates to a process for amplifying existing nucleic acid sequences present in a nucleic acid or mixture thereof using primers and agents for polymerization, and then detecting the amplified sequence. See Col. 1, lines 15-18 and Col. 2, lines 45-49. Mullis does not teach or suggest the quantitation of a target RNA sequence, or a kit specifically intended for quantitation of a target RNA sequence by use of an internal control sequence.

Example 2 of the Mullis patent, which is the primary basis for the rejection, describes the amplification of a 94-base pair sequence contained within the human β-globin gene. In the experiment, two oligonucleotide primers (A and B) were added to a reaction mixture containing nucleotide precursors and other reagents. Five different reaction mixtures (Reactions I-IV) were prepared with each reaction mixture containing a single different source of DNA, i.e., wild-type DNA, pBR328:HbA, pBR328:HbS, pBR328:HbA/MstII, and pBR328:HbS/MstII.

See Col. 22, line 56 to Col. 23, line 3. A Reaction VI contained no target DNA. Each resulting solution (Reactions I-VI) was then separately subjected to the steps of the polymerase chain reaction. See Col. 23, lines 4-56.

Of these reactions, the Examiner asserts that the amplified target sequences pBR328:HbA and pBR328:HbS "serve as control sequences compared to the MstII restriction enzyme digested plasmids . . . . " See Office Action at p. 13, lines 14-22. However, the Mullis patent, in referring to Figure 3, expressly states that Reaction VI, which contained no DNA, served as the control sequence for the experiment:

> Another lane for Reaction VI with no DNA as control had no images in any of the lanes. It can be seen from the figure [Figure 3] that the 94-bp fragment predicted from the target DNA was present only where intact β-globin DNA sequences were available for amplification, i.e., pBR328:HbA (Lane 2), pBR328:HbS (Lane 3) and pBR328:HbS/MstII (Lane 5). MstII cuts pBR328:HbA in the 94-mer sequence rendering it incapable of being amplified, and the 94-mer band does not appear in Lane 4.

Col. 23, line 60 to Col. 24, line 1. The target sequences were in fact pBR328:HbA, pBR328:HbS and pBR328:HbA/MstII, as shown in Lanes 2, 3 and 5 of the electrophoresis gel, respectively. Mullis neither discloses nor contemplates use of an internal standard or control sequence to allow the quantitation of the amount of target RNA sequence after amplification. Further, the fact that the target nucleic acid sequences in Example 2 were of predetermined quantities serves no purpose other than to establish a volumetric consistency between the separate reactions. Mullis does not disclose or suggest use of a "predetermined initial amount of a control sequence" for quantitation of a target RNA, as required by claim 36.

A publication anticipates a claim if the publication discloses each and every limitation, or element, of the claim. See, e.g., Gechter v. Davidson, 116 F.3d 1454, 1457 (Fed. Cir. 1997). Therefore, absent each and every limitation of the claim in question, disclosed either literally or inherently, a reference is not anticipatory. Because the Mullis patent does not disclose a kit containing a predetermined amount of a reference or control sequence and a primer pair used for the quantitation of a target RNA segment, the Mullis patent does not anticipate claim 36. Claim 40 (wherein the control sequence is a maxigene), which depends from claim 36, is likewise not anticipated by the Mullis patent.

Independent claim 37 is directed essentially to a plasmid for use as an internal control for quantitation of a target RNA sequence, comprising a control sequence having two sequences which provide primer hybridization sites in the plasmid that are identical to primer hybridization sites within the target RNA sequence such that a primer pair will function in the PCR reaction to amplify the control sequence and the target RNA segment, wherein upon amplification the control sequence and the target segments can be distinguished by size.

While the Mullis reference may disclose PCR amplification primers synthesized for pBR328 segment amplification, and that various reaction mixtures may be prepared using a set of primers mixed with different target nucleic acids, Mullis does not disclose a plasmid used as an internal control for quantitation of a target RNA sequence, wherein upon amplification the control sequence and the target segments can be distinguished by size. Therefore, each and every element claim 37 is not found in the Mullis reference, and it does not anticipate claim 37.

Claim 41 (maxigene control sequence), which depends from claim 37, is likewise not anticipated by the Mullis patent.

Independent claim 48 is directed essentially to the same subject matter as claim 37, except that claim 48 includes the further limitation that upon amplification the control sequence and the target segments can be distinguished by use of an internal oligonucleotide probe. Mullis does not anticipate claim 48 for the same reasons as claim 37.

Therefore, Applicants believe that rejection has been obviated by the amendments discussed above, and respectfully request that it be reconsidered and withdrawn.

E. Rejection Under 35 U.S.C. § 103(a)

Claims 36 and 40 were rejected under 35 U.S.C. § 103(a) as obvious over U.S. Patent 4,683,195 to Mullis et al. ("Mullis") in view of an excerpt from the 1988 Stratogene Catalog, p. 39.

The Examiner asserts that Mullis discloses PCR amplification primers and control nucleic acids and acknowledges that Mullis does not disclose a kit per se. See Office Action at p. 15, lines 26-29. However, it is the Examiner's position that the disclosure of the Stratogene Catalog "motivates and suggests that the assemblage of materials into kits which may be pre-mixed for the benefits therein cited such as availability and quality testing etc." Id at lines 30-33. This rejection is respectfully traversed. In the absence of a prior art teaching of the use of a control sequence for the quantitation of a target sequence following amplification, there was no motivation to assemble a control sequence and primer pair in kit form.

The Stratogene Catalog describes gene characterization kits providing materials for specifically defined experiments, including materials "to map, sequence, transcribe, translate, cap, or hybridize nucleic acids." According to the Catalog, each kit provides two services: (1) a variety of different reagents assembled and pre-mixed *specifically for a defined set of experiments*, and (2) a measure of quality control via Stratogene's testing of the components of a kit prior to sale. Stratogene Catalog, at p. 39 (emphasis added). Nowhere on page 39 of the Catalog does it teach or suggest that the Stratogene kits are useful for PCR amplification and/or quantitation of target RNA segments, or that the kits could be used to provide a predetermined initial amount of a control sequence for quantitation of a target RNA and an oligonucleotide primer pair wherein the primer pair can serve to amplify the control sequence and the target RNA. Rather, the Stratogene kits are described as merely useful "for a defined set of experiments," e.g., DNA and RNA sequencing. In the absence of any suggestion of the above elements in the Stratogene reference, the reference cannot suggest the combination of elements set forth in claim 36. Claim 40 (maxigene control sequence), which depends from claim 36, is likewise not suggested by the Stratogene Catalog reference.

Applicable case law holds that in order for a combination of prior art references to render claims obvious, the prior art must contain at least some suggestion of the features in the claim at issue. In the complete absence of any suggestion of the features of the claimed invention as set forth above, it is respectfully submitted that the Stratogene Catalog reference is not properly combinable with the Mullis patent and does not render claims 36 or 40 obvious.

Therefore, Applicants believe that rejection has been obviated by the amendments discussed above, and respectfully request that the rejection be reconsidered and withdrawn.

F. Rejection Under 35 U.S.C. § 101 (Double Patenting)

The Examiner entered a provisional, statutory double patenting rejection under 35 U.S.C. § 101 against claims 34-45. In particular, the Examiner asserts that claims 34-45 are directed to the same subject matter as that of claims 31-42 of copending Application Serial No. 08/769,584, which is a divisional application of the present application.

Upon an indication of allowable claims in the present application, Applicants will cancel or amend any conflicting claims in Application Serial No. 08/769,584 so they are no longer coextensive in scope.

G. Rejection Under the Doctrine of Obviousness-Type Double Patenting

The Examiner entered a provisional rejection of claims 46-49 under the doctrine of obviousness-type double patenting. In particular, the Examiner asserts that claims 46-49 are directed to substantially the same subject matter as that of claims 31-42 of copending Application Serial No. 08/769,584, and states that a timely filed terminal disclaimer may be used to overcome the rejection.

Upon an indication of allowable claims in the present application, Applicants will submit a terminal disclaimer with respect to claims 31-42 in copending Application Serial No. 08/769,584.

**Concluding Remarks**

In view of the foregoing, favorable reconsideration of this application is respectfully requested. In the event that any additional fees are due in relation to this document, please charge our Deposit Account No. 02-2135.

Respectfully Submitted,

By _____

Jeffrey W. Rennecker
Attorney for Applicants
Registration No. 40,784
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
555 13th Street, N.W., Suite 701-E
Washington, D.C. 20004
Telephone: (202) 783-6040

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